Case Report

Hemodialysis for removal of dabigatran in a patient with gastric hemorrhage

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Case: An 82-year-old man taking dabigatran was admitted with syncope. Computed tomography showed extravasation from the stomach. Laboratory data revealed renal insufficiency and prolonged activated partial thromboplastin time. The gastric endoscopy showed a gastric ulcer with an exposed vessel. However, an endoscopic hemostatic procedure failed to completely stop the bleeding. The patient experienced cardiac arrest from hypotensive shock. Spontaneous circulation returned after 5 min of resuscitation. After endoscopy, computed tomography showed a gastric perforation. For dabigatran removal, the patient underwent a 6-h hemodialysis session. Thrombin activity and thrombin–antithrombin complex increased during hemodialysis, while activated partial thromboplastin time decreased.

Outcome: Good recovery was observed after dialysis and the following gastrectomy.

Conclusion: Hemodialysis should be considered for dabigatran removal in cases of life-threatening hemorrhage. The thrombin–antithrombin complex may be useful for monitoring the plasma dabigatran level.

Key words: Anticoagulants, dabigatran etexilate, hemorrhage, peptic ulcer perforation, renal dialysis

INTRODUCTION

DABIGATRAN ETEXILATE (DABIGATRAN) is a direct thrombin inhibitor approved in the USA for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (AF) as well as for the treatment and risk reduction of deep vein thrombosis (DVT) and pulmonary embolism (PE) recurrence.[1] The RE-LY trial showed similar thromboembolism rates and lower major hemorrhage rates with dabigatran (110 mg twice daily) compared with warfarin in patients with AF.[2] Furthermore, in patients with DVT and PE, the RE-COVER and RE-COVER II trials indicated that dabigatran is not inferior to warfarin for reducing DVT and PE and was associated with lower overall bleeding rates.[1] Moreover, unlike warfarin, dabigatran does not require routine coagulation monitoring and subsequent dose adjustments.

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However, the risk of major bleeding is still present and requires adequate treatment. There is no antidote to rapidly reverse the effects of dabigatran. Fresh frozen plasma, recombinant activated factor VIIa, and prothrombin complex concentrates (PCC) may be effective; however, their efficacy has not been established.[3] Owing to low protein binding, hemodialysis is recommended for major bleeding complications with dabigatran.[3]

Here, we present a case of an elderly man taking dabigatran who presented with a fatal hemorrhagic gastric ulcer and underwent hemodialysis to decrease the plasma dabigatran level.

CASE

AN 82-YEAR-OLD MAN who was taking dabigatran (110 mg twice daily) for AF presented with syncope and melena. He had taken dabigatran 4 h prior to admission.

His pulse rate was 80 b.p.m. and blood pressure was 118/80 mmHg. The palpebral conjunctiva was pale, and his abdomen was soft, with no tenderness. Bright red blood was sucked through a nasogastric tube. Enhanced computed tomography (CT) of the abdomen showed contrast extravasation at the upper body of the stomach. Laboratory findings

Table 1. Transition of coagulation markers during a 6-h hemodialysis session for removal of dabigatran in an 82-year-old man with gastric hemorrhage

Markers			During dialysis		
	Reference range	On admission	0 min†	180 min	360 min‡
PT, %	75.0–120.0	48.9	50.5	70.0	80.9
aPTT, s	24.0–39.0	46.5	61.7	66.1	38.0
Thrombin activity, %	66.0–118.0	NA	57.6	70.1	72.2
TAT, μg/L	1.0–4.1	NA	5.9	10.6	44.0

†High-flux hemodialysis was initiated with no anticoagulant 5 h after admission (9 h after last dabigatran use). ‡Hemodialysis was completed at 360 min. aPTT, activated partial thromboplastin time; PT, prothrombin time; TAT, thrombin–antithrombin complex; NA, not available.

were as follows: hemoglobin, 7.6 g/dL; hematocrit, 22.3%; platelets, $97 \times 10^3/\mu L$; prothrombin time (PT), 48.9%; activated partial thromboplastin time (aPTT), 46.5 s; fibrinogen, 193 mg/dL; serum creatinine, 1.5 mg/dL (estimated glomerular filtration rate, 35.1 mL/min/1.73 m^2); blood urea nitrogen, 42 mg/dL.

Gastrointestinal endoscopy showed peptic ulcer bleeding from an exposed vessel at the anterior wall of the upper gastric corpus. Clip devices could not completely stop the bleeding, and the patient experienced cardiac arrest from refractory shock with massive bleeding. Spontaneous circulation returned 5 min after cardiopulmonary resuscitation including intubation and a 1-mg epinephrine injection. At this point, he had received 16, 12, and 20 units of packed red blood cells, fresh frozen plasma, and platelet concentrates, respectively. After endoscopy, non-contrast CT revealed intra-abdominal free air consistent with gastric perforation.

For dabigatran removal, hemodialysis was initiated using a polysulfone dialyzer with 150 mL/min blood flow 5 h after admission (9 h after last dabigatran use). During the dialysis treatment, no anticoagulant was used, and thrombin activity, thrombin–antithrombin complex (TAT), PT, and aPTT were monitored, with aPTT as a marker of serum dabigatran levels. Blood samples were drawn before and 3 and 6 h after initiation. Six hours after dialysis initiation, aPTT decreased to within the normal range, and the dialysis column was clogged with clot formation. Coagulability appeared to be normalized clinically, and hemodialysis was ceased. Thrombin activity and TAT increased from 57.6 to 72.2% and 5.9 to 44 μg/L, respectively, during hemodialysis (Table 1).

After dialysis, the gastric perforation was repaired by subtotal gastrectomy. There was no intraoperative bleeding tendency or postoperative progression of anemia. The patient was extubated on postoperative day 4 and required an additional 6 days of non-invasive negative pressure ventilation for aspiration pneumonia. He was discharged from the hospital 56 days after admission without any cognitive disorder.

DISCUSSION

THE PRESENT PATIENT was treated successfully with hemodialysis for dabigatran removal following a dabigatran-associated fatal gastric hemorrhage. Dabigatran etexilate is rapidly absorbed and metabolized by esterase to produce dabigatran and acyl glucuronide.[4] Following oral administration, the maximum concentration is achieved at 2–3 h, and the elimination half-life is 12–17 h.[4] Eighty-five percent of plasma dabigatran is excreted through the kidneys, which is prolonged with renal insufficiency.[5] In the present patient, the pre-admission renal function was unknown; however, the massive hemorrhage from the gastric ulcer was likely affected by prolonged dabigatran excretion resulting from renal insufficiency with hypovolemic shock.

Dabigatran inhibits platelet aggregation and thrombus formation in the thrombin-induced coagulation cascade. It is difficult to reverse the anticoagulation effect of dabigatran because a specific antidote is lacking. Activated charcoal given orally has been shown to be effective; it should be administered within 1–2 h after dabigatran intake, before dabigatran is absorbed into the intestine.[3] Fresh frozen plasma, recombinant activated factor VIIa, or PCC might also reverse the anticoagulation effect.[3] Recombinant activated factor VIIa antagonized the anticoagulant effect and PCC reduced dabigatran-associated bleeding time in healthy volunteers and in *in vitro* investigations;[3] however, a controlled clinical trial showed that PCC was not effective in reversing the anticoagulative effect.[6]

Due to low protein binding, hemodialysis can remove dabigatran.[7] An open-label study showed that two-thirds of dabigatran was removed by a 2-h hemodialysis session in six patients with end-stage renal disease on maintenance

hemodialysis who were taking 50 mg dabigatran daily;[5] however, this dose is lower than the typical dose (110 or 150 mg twice daily). Therefore, longer hemodialysis sessions may be required for overdose or severe bleeding.[7]

It is difficult to monitor the effect of dabigatran in clinical practice. Activated partial thromboplastin time and PT, which are the commonly available assays to assess anticoagulation, lack adequate sensitivity to differentiate subtherapeutic, therapeutic, and supra-therapeutic dabigatran concentrations.[8] Thrombin time is the most sensitive test for dabigatran-related anticoagulation and is useful in detecting the presence of dabigatran in circulation, but is too sensitive to differentiate therapeutic from supra-therapeutic concentrations. Therefore, it is also inappropriate for monitoring patients with hemorrhage.[8]

In the present case, thrombin activity, TAT, aPTT, and PT were measured. While aPTT decreased, thrombin activity and TAT increased. The increased thrombin activity was related to the decreased dabigatran concentration; thrombin is rapidly inactivated by complex formation with antithrombin III. Thrombin activation and fibrin formation subsequently elevate TAT.[9] Therefore, the measurement of TAT could act as a marker of dabigatran removal during hemodialysis.

This case study has several limitations. Although the findings of thrombin activity and TAT suggest that hemodialysis can remove dabigatran, the serum dabigatran level was not measured. Furthermore, the correlation between TAT and plasma dabigatran level is not known, and TAT and aPTT are qualitative, rather than quantitative, markers.

CONCLUSION

ALTHOUGH FREQUENT MONITORING of coagulation with dabigatran is not required, unlike with warfarin, life-threatening hemorrhage can occur; hemodialysis should be considered for dabigatran removal in this situation. Monitoring the effect of dabigatran on coagulation can be difficult. However, the measurement of TAT may be useful to monitor dabigatran removal.

CONFLICT OF INTEREST

NONE.

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